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Edoxaban for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

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Abstract

Introduction Oral anticoagulation is central to the management of patients with atrial fibrillation (AF) and at least one additional stroke risk factor. For decades, the vitamin K antagonists (e.g. warfarin) remained the only oral anticoagulant available for stroke prevention in AF. The non-vitamin K oral anticoagulants (NOACs) are now available, and these drugs include the direct thrombin inhibitors and factor Xa inhibitors. The latter class includes edoxaban that has recently been approved for stroke prevention in AF by United States Food and Drug Administration and European Medicine Agency. In line with other NOACs, edoxaban avoids the many limitations of warfarin associated with variability of anticoagulation effect and multiple food and drug interactions.

Areas covered In this review, the currently available evidence on edoxaban in patients with non-valvular AF is discussed. The pharmacology, efficacy and safety, and current aspects of use of edoxaban in patients with non-valvular AF for stroke and thromboembolism prevention are reviewed.

Expert opinion Phase III trial on edoxaban for stroke prevention in non-valvular AF confirms non-inferiority of edoxaban compared to well-managed warfarin both in terms of efficacy and safety. Currently ongoing and future trials as well as real-world data are warranted to confirm its effectiveness and safety for chronic anticoagulation and improve evidence in other areas which are lacking evidence where NOAC use remains controversial.

Key words: edoxaban, warfarin, oral anticoagulation, atrial fibrillation, efficacy, safety.

1. Introduction

Cardiovascular diseases are frequently associated with thrombotic complications, e.g., stroke, pulmonary embolism, acute coronary syndrome, which together result in high disability and mortality rate. There were 5.9 million stroke deaths recorded in the 2010 worldwide, half of which were due to ischaemic stroke caused by thrombosis. This represents a 25% increase during the two decades and the trend is likely to be continued [1].

Atrial fibrillation (AF) is the most common sustained arrhythmia affecting 1-3% of general population steadily rising in an age-dependent manner. AF is one of major contributors to stroke morbidity and mortality by increasing the risk of stroke five-fold [2, 3]. Moreover AF is often asymptomatic, and often diagnosed opportunistically or only after presentation with a complication, such as stroke or heart failure; hence, the real prevalence of AF is likely to be even higher [4]. The absence of clinical symptoms of arrhythmia does not necessarily mean lower stroke risk, resulting in asymptomatic patients being at particular risk because of absence of timely initiated antithrombotic therapy. As a result AF is often diagnosed after stroke has already developed, or remains undiagnosed if paroxysms of arrhythmia are short and infrequent [5].

Stroke and systemic embolism (SE) prevention with oral anticoagulation (OAC) is the mainstay of AF management. Lone AF carries a low risk of stroke and represents the minority of patients for whom OAC is not indicated because of low stroke risk, and the benefits of stroke prevention with OAC are not outweighed by increased risk of bleeding [6]. The vast majority of AF patients have one or more additional stroke risk factors, including heart failure, arterial hypertension, diabetes mellitus, previous history of stroke or transient ischaemic attack, atherosclerotic arterial disease, age and female gender, which were jointly combined in the CHA_2DS_2-VASc score (Table 1) [7-9]. With 1 stroke risk factor, the stroke risk increases from 0.04-2.4 %/year to 0.55-6.6 %/year and this should trigger initiation of OAC [10]. Female gender is considered as stroke

risk factor only in conjunction with another risk factor, i.e. the CHA_2DS_2-VASc score = 2 is the threshold for OAC in females [11].

To minimize probability of bleeding with OAC, especially major bleeds, risk of bleeding has to be assessed as well, e.g. with the HAS-BLED score (Table 1) [7, 8, 12]. Stroke and bleeding risk factors overlap, but higher bleeding risk results into higher net clinical benefit of OAC [13]. Hence, a high HAS-BLED score (≥3) should not be used to rule out eligible patients for OAC based on stroke risk assessment but to control modifiable risk factors appropriately.

Anticoagulant therapy is available as vitamin K antagonists (VKAs), e.g. warfarin, and non-VKA oral anticoagulants (NOACs) [14]. Despite being the 'all-purpose' oral anticoagulant with the longest experience in various clinical settings, warfarin remains an 'inconvenient' drug both for patients and physicians due to its slow onset and offset of action, variability of anticoagulation effect, as determined by genetic polymorphism of enzymes, multiple food and drug interactions, etc. – leading the requirement to stay in a narrow therapeutic window of international normalized ratio (INR) of 2.0-3.0 that needs to be monitored regularly.

On the contrary NOACs allow us to overcome major drawbacks of warfarin, i.e. they offer fast, predictable and stable anticoagulation effect with a fixed dose without need for laboratory monitoring and minor food and drug interactions [15, 16]. Currently approved NOACs include direct thrombin inhibitor dabigatran and factor Xa inhibitors apixaban, rivaroxaban, and edoxaban.

The current review is focused on the pharmacology, efficacy and safety of factor Xa inhibitor edoxaban that is the latest NOAC approved by the European Medicines Agency (EMA) and

United States Food and Drug Administration (FDA) as well as in Japan and Switzerland for stroke and SE prevention in non-valvular AF.

2. Pharmacology of edoxaban

The coagulation cascade includes extrinsic pathway that is activated by exposure of blood to tissue factor. It results in synthesis of a small amount of thrombin, but the latter allows amplification of intrinsic pathway via activation of a variety of factors in the coagulation cascade (e.g., factors V, VIII, XI, XIII) and synthesis of greater amount of thrombin [17].

Edoxaban rapidly and selectively inhibits enzymatic activity of factor Xa, key enzyme located at the confluence of the intrinsic and extrinsic coagulation pathways (common pathway). It binds to free factor Xa, factor Xa within prothrombinase complex as well as clot-associated factor Xa that eventually leads to downstream dose-dependent blockade of prothrombin to thrombin conversion [18]. One inhibited molecule of factor Xa prevents conversion of approximately 1000 molecules of prothrombin to thrombin [15].

Direct factor Xa inhibition also offers pleiotropic effects not related to anticoagulation per se. Factor Xa contributes to atherosclerosis via the activation of proteinase-activated receptors PAR-1 and PAR-2 signalling as well as tissue factor expression in vascular endothelial cells and smooth muscle cells, synthesis of inflammatory cytokines such as interleukin-6, tumor necrosis factor-α, and monocyte chemoattractant protein-1, abnormal cell proliferation and extracellular matrix accumulation [18, 19]. Thus, factor Xa inhibition in experimental works resulted in abrogation of aforementioned mechanisms towards slowing of atherosclerosis progression and stabilization of advanced atherosclerotic plaques. Edoxaban and other NOACs do not cause vascular calcification because of no effect on matrix Gla-protein (MGP) as VKAs do [19].

Edoxaban is supplied as edoxaban tosylate monohydrate. In studies on pharmacokinetics and pharmacodynamics of edoxaban it was found to be rapidly absorbed predominantly in the proximal small intestine with an oral bioavailability of 61.8%, 95% confidence interval (CI) 57.7-66.2% in healthy adults [20, 21].

Peak plasma concentration (C_{max}) and peak anti-factor (F)Xa activity of 2.68 IU/mL was achieved in approximately 1.5 hours, furthermore prothrombin fragment 1+2, thrombin-antithrombin complex, and platelet activation marker β-thromboglobulin are all were reduced, indicating inhibition of thrombin generation and platelet activation. There was also close correlation with prothrombin time (PT), followed by INR and activated partial thromboplastin time (aPTT). Sustained inhibition of coagulation after oral administration above baseline level is observed for up to 24 hours [22-25]. The terminal half-life of edoxaban 60 mg is 10 to 14 hours [26].

Unchanged edoxaban is the predominant form in plasma, and over 70% is excreted unchanged. There is minimal metabolism via hydrolysis mediated by carboxylesterase-1 with formation of major metabolite M4, and also conjugation, and oxidation by CYP3A4. 62.2% of edoxaban are eliminated in faeces and 35.4% - in urine [27]. Notwithstanding the role of the kidneys in the elimination of edoxaban and its relatively low protein binding in patients with end stage renal disease, edoxaban exposure is not affected by haemodialysis [28].

Patients gender and ethnicity as well as food intake were shown to have no effect on pharmacology of edoxaban [29, 30] while low body weight, i.e. 60 kg or lower, was associated with higher trough edoxaban concentration (C_{min}) and, eventually, higher rate of bleeding complications [31, 32].

Edoxaban is a substrate of P-gp (permeability glycoprotein) efflux transporter in the intestine but not of other major uptake transporters, e.g. OAT1, OAT3, OCT1, OCT2, OATP1B1, and OATP1B3, resulting in drug-drug interactions of P-gp inducers and inhibitors [27, 33]. When co-administered with a P-gp inhibitor quinidine, area under time-concentration curve (AUC) and C_{max} of edoxaban increased by 76.7% and 85.4%; dronedarone - 84.5 and 45.8 %, verapamil - 52.7 and 53.3, amiodarone - 39.8% and 66.0%, respectively [34]. Combination of digoxin with edoxaban results in minor increase of AUC and C_{max} of the latter - by 9.5 and 15.6%, respectively, while atorvastatin caused increase of AUC of edoxaban by 1.7% and a decrease of C_{max} by 14.2% [34].

P-gp inducer rifampin was found to reduce oral bioavailability of edoxaban and to increase its excretion through induction of P-gp. Metabolism of edoxaban with synthesis of its metabolite M6 (through CYP3A4/5) and M4 (due to the inhibition of OATP1B1 and induction of carboxylesterase-1) was increased. Overall concomitant administration of rifampin with edoxaban resulted in an approximate 34 % decrease in total exposure to edoxaban but three-fold increase in exposure to its metabolites [35].

Pharmacological characteristics of edoxaban are summarized in the Table 2. Edoxaban with respect to its pharmacological characteristics is broadly similar to other factor Xa inhibitors and direct thrombin inhibitor dabigatran etexilate (e.g., time to maximum plasma concentration, half-life time, interactions with drugs which affect P-gp transporter). One of the most important characteristics that makes NOACs different and should be considered in clinical practice is a renal clearance, that is the highest for dabigatran (80%); edoxaban is half-cleared by kidneys (50%) while renal clearance of apixaban and rivaroxaban is 27% and 35%, respectively [6, 15].

3. Edoxaban trials

In a safety, tolerability, pharmacokinetic, and pharmacodynamic phase I study of edoxaban healthy adults were administered range of doses – either single dose (n=85) of 10 to 150 mg once daily (qd) or multiple doses (n=36) of 90 and 120 mg qd, 60 mg twice daily (bid). Both single and multiple doses were well tolerated. There were no dose-dependent increase in treatment-emergent adverse events, of which majority were mild, and no serious adverse events were observed [22].

Two phase II dose-ranging studies were performed, randomized AF patients who required OAC for stroke prevention, to double-blind edoxaban and open-label dose-adjusted warfarin (INR 2.0–3.0) arms. In the study by Weitz et al. four dosing regimes of edoxaban were tested: 30 mg qd, 30 mg bid, 60 mg qd, 60 mg bid, in predominantly Caucasian population (n=1146) while Yamashita et al. tested three regimes: 30 mg qd, 45 mg qd, and 60 mg qd, in 536 Asian AF patients [31, 36]. Patients were followed-up for twelve weeks. The major and consistent finding from both studies was that qd regime of edoxaban administration was safer in terms of major and clinically relevant non-major bleeding, and no differences were observed between edoxaban and warfarin arms [31, 36]. On the contrary, twice a day regimes of edoxaban were both associated with significantly higher bleeding rate compared to warfarin. For example in the study of Weitz et al. major and clinically relevant non-major bleeding occurred in 3.2% of patients randomized to warfarin, 3.8% and 3.0% in edoxaban 60 mg qd and 30 mg qd, respectively, versus 10.6% and 7.8% in edoxaban 60 mg bid and 30 mg bid, respectively [36].

These data was further confirmed in the pooled population pharmacokinetic analysis of phase I and phase II studies to support dose selection for a phase III study. Moderate renal impairment and concomitant strong P-gp inhibitors were found to be the main factors influencing on the

pharmacokinetics of edoxaban with the necessity to reduce the dose by 50%. Steady-state concentration of edoxaban showed the strongest association with the bleeding events [37]. Given that C_{min} is higher with bid regime, edoxaban 30 mg qd (low dose) and 60 mg qd (high dose) as well as reduced based on patients characteristics to 15 mg qd and 30 mg qd dosing regimes were chosen for the phase III trial [37].

The ENGAGE AF – TIMI 48 (Effective anticoagulation with factor xa next generation in atrial fibrillation – thrombolysis in myocardial infarction 48) trial was the largest multinational phase III study with randomized, non-inferiority, double-blind, double-dummy design, compared efficacy and safety of two doses of edoxaban against dose-adjusted warfarin in patients with non-valvular AF (Table 3) [38, 39]. Thus, the ENGAGE AF – TIMI 48 had the same design as other phase III trials with factor Xa inhibitors (e.g., rivaroxaban and apixaban) while the RE-LY trial with dabigatran was open label between dabigatran and warfarin arms, but double blind between 2 arms with different doses of dabigatran. Patient cohorts among the NOACs trials had some differences that might affect interpretation of trial results [40]. For example, patients involved in the ENGAGE AF – TIMI 48 trial had mean $CHADS_2$ of 2.8 that was higher than in the trials with dabigatran and apixaban (2.1), but lower than in trial with rivaroxaban (3.5). The latter corresponds to history of stroke among study participants [6, 15]. Patients in the ENGAGE AF – TIMI 48 trial had the highest time in therapeutic range in warfarin arms and discontinuation rate compared to other NOACs trials [6, 15].

The dose was halved if any of the following characteristics were present at the time of randomization or during the study: creatinine clearance (CrCl) of 30 to 50 ml/min, a body weight of ≤60 kg, or the concomitant use of potent P-gp inhibitors (verapamil, quinidine, or dronedaron) [39]. Patients with $CHADS_2$ score ≥2 were included. The median duration of follow-up was 2.8

years. In the warfarin arm there was good quality anticoagulation control with median time in therapeutic range (TTR) of 68.4% (interquartile range 56.5 to 77.4) [39].

In terms of efficacy both edoxaban regimes were found to be non-inferior to warfarin in the intention-to-treat analysis [39]. There was a trend toward better efficacy of high dose edoxaban versus warfarin for stroke and SE prevention (hazard ratio [HR] 0.87, 97.5% CI 0.73–1.04) that was lacking for low-dose edoxaban. In an on-treatment analysis, high dose edoxaban was more effective than warfarin (HR 0.79; 97.5% CI 0.63 to 0.99) [39]. When both ischaemic and haemorrhagic strokes were analyzed in an on-treatment analysis high dose edoxaban was also superior to well managed warfarin (HR 0.80, 95% CI 0.65–0.98) [41].

Importantly, both dosing regimes of edoxaban were associated with reduced cardiovascular mortality: HR 0.86, 95% CI 0.77–0.97, and HR 0.85, 95% CI 0.76–0.96, for edoxaban 60 mg qd and 30 mg qd, respectively. There was also a borderline reduction of all-cause mortality with high dose edoxaban (HR 0.92, 95% CI 0.83–1.01) that reached significance with low dose edoxaban (HR 0.87, 95% CI 0.79–0.96) [39].

In terms of safety outcomes, both edoxaban dosing regimes were associated with significantly lower risk of bleeding events compared to warfarin, including major, major plus clinically relevant non-major bleeding, intracranial haemorrhage (ICH), and any bleeding [39]. Gastrointestinal bleeding was less frequent with edoxaban 30 mg qd, but more frequent with edoxaban 60 mg qd [39].

Noteworthy, development of a transition protocol from blinded edoxaban to open warfarin or from blinded warfarin to open warfarin at the end of the ENGAGE AF – TIMI 48 trial allowed

to avoid excessive rates of stroke or major bleeding as it was seen in the ROCKET AF trial with rivaroxaban and the ARISTOTLE with apixaban [42, 43].

Edoxaban was shown to perform equally in majority of subgroups specified according to age, gender, body weight, stroke risk, etc. (Table 4). However there was a significant interaction between efficacy of edoxaban and kidney function. In patients with mild kidney dysfunction (CrCL of 50 to 80 ml/ min) edoxaban 60 mg qd was found to reduce the risk of stroke and SE (HR 0.51, 95% CI 0.38-0.69) while in patients with normal CrCl of 80 ml/min or more the risk of stroke and SE was higher than in patients on warfarin (HR 1.41, 95% CI 0.97-2.05) [44]. Results were also worse for other end points such as ischaemic stroke (HR 0.62, 95% CI 0.43-0.87 versus HR 1.58, 95 % CI 1.02-2.45, in patients with mild kidney dysfunction and normal function, respectively) and cardiovascular mortality (HR 0.75, 95% CI 0.62-0.90 versus HR 1.15, 95 % CI 0.91-1.45, in patients with mild kidney dysfunction and normal function, respectively) [44]. Edoxaban 30 mg qd was associated even with greater risk of stroke and SE compared to warfarin.

When further subdivided into groups according to CrCl cut off value of CrCl of 95 ml/min was found, for which edoxaban provided the efficacy similar to dose-adjusted warfarin (HR 1.02, 95% CI 0.76-1.38). In patents with CrCl >95ml/min the risks of stroke and SE were in favor of warfarin therapy [44]. The poorer outcomes in patients with normal kidney function with edoxaban were suggested to be due to lower drug exposure given kidney clearance of edoxaban of 50%.

However, interpretation of this finding has to be cautious, since it could be affected by range of facts, e.g., low number of events and patients with normal kidney function, demographic characteristics (lower stroke risk and younger age if patients with normal kidney function

compared to those with reduced one), good quality of anticoagulation with warfarin resulted in unexpectedly low rate of events in warfarin arm [45]. Assessment of rate of stroke and SE in patients on edoxaban also did not support low efficacy of edoxaban in patients with normal kidney function. It tended to increase from the lowest in patients with normal kidney function (1.26% per year) to mild and moderate kidney dysfunction (1.49% and 2.29% per year, respectively) [45].

Apparently, drug exposure affects clinical outcomes. In patients treated with dabigatran within the RE-LY (Randomized evaluation of long-term anticoagulation therapy) trial, over 5-fold variability of plasma concentration was observed that translated into concentration-dependent increase of bleeding complications, however risk of thromboembolic events appeared to be less dependent on concentration variability [46, 47].

An analysis of the ENGAGE AF – TIMI 48 trial data was performed to assess whether adjustment of dose of edoxaban based on patients characteristics applied in the trial was sufficient alone to assure stable plasma concentrations, and eventually, anticoagulant (anti-FXa) activity as well as stroke/SE and bleeding events. Reduction of edoxaban dose from 60 mg qd to 30 mg qd decreased mean exposure by 29% (from 48.5 ng/ml to 34.6 ng/ml) and anti-FXa activity by 25% (from 0.85 IU/mL to 0.64 IU/ml). In the low dose edoxaban arm, concentration decreased by 35% (from 24.5 ng/ml to 16.0 ng/ml) and anti-FXa activity by 20% (from 0.44 IU/ml to 0.35 IU/ml). Overall across all used dosing regimes three-fold and 2.4-fold variability of trough plasma concentration and anti-FXa activity was seen [48].

Greater than expected reductions of concentration and anticoagulant effect however did not result in higher stroke/SE rate but ensured lower risk of bleeding [48]. Consistent with the dabigatran data [47], with increasing edoxaban concentration, a gradual, linear decrease in the

risk of stroke and SE events but steeper increase in the risk of major bleeding was observed [48]. Of note, a low probability of ICH with a relatively flat association was seen across edoxaban concentrations [48] in contrast to VKAs which are known to increase the risk of ICH in exponential manner with increasing anticoagulation intensity [49].

In another pre-specified analysis impact of amiodarone administered concomitantly was studied [50]. Due to P-gp inhibition amiodarone results in increased edoxaban plasma concentration. The results of this study complemented the last one on drug concentration and efficacy and safety outcomes interplay. Amiodaron co-administration in patients taking low dose edoxaban led to significantly lower rate of the primary efficacy endpoint compared with warfarin versus patients not on amiodarone (HR 0.60, 95% CI 0.36–0.99, and HR 1.20, 95% CI 1.03–1.40, respectively; p for interaction <0.01), but it did not influence on major bleeding risk [50]. In patients taking high dose edoxaban amiodarone co-administration affected neither risk of stroke and SE nor rate of major bleeding [50]. Nonetheless these patients experienced more major and clinically relevant non-major bleedings compared with warfarin versus patients on high dose regime of edoxaban without amiodarone concomitantly (HR 1.12, 95% CI 0.91–1.36 versus HR 0.83, 95% CI 0.77–0.89, p for interaction 0.008) [50]. Suggested by Steffel et al explanation for this was based on clinical outcomes – drug concentration curves, e.g., increase in concentration of edoxaban against a low dose regime due to amiodarone occurred in steeper part of the curve for stroke or SE resulting in improvement of efficacy while shift of edoxaban concentration with a high dose regime of edoxaban with amiodarone concomitantly appeared to be within flat part of the curve. Vice versa, increase in concentration of edoxaban against a low dose regime due to amiodarone occurred in flat part of the curve for major bleeding but in steeper part with a high dose edoxaban regime [50].

Finally, pre-specified echocardiographic analysis of left atrial structure and function was performed among the ENGAGE AF – TIMI 48 participants [51]. Left atrial remodeling is a cornerstone of AF pathogenesis [52]. Despite indices of left atrial structure and function have not been implicated yet into decision making process with respect to anticoagulation management on a routine basis they carry important information. Left atrial fibrosis was found to be associated with the $CHADS_2$ score and stroke risk and even improved performance of stroke risk scores in several studies [52]. The analysis of echocardiographic data from the ENGAGE AF – TIMI 48 trial also revealed relationship between left atrial dysfunction and the $CHADS_2$ score. Moreover left atrial contractile dysfunction was observed in AF patients on sinus rhythm during examination that supported stroke prevention with OAC irrespectively of AF type [51].

4. Regulatory affairs

Ministry of Health, Labour and Welfare in Japan was the first regulatory authority that approved edoxaban for stroke and SE prevention in patients with non-valvular AF following announcement of results of ENGAGE AF – TIMI 48 trial (September 26, 2014) [53].

For the same indication edoxaban 60 mg qd in patients with CrCl >50 to ≤95 mL/min with dose reduction to 30 mg qd in patients with CrCl of 15 to 50 mL/min gained approval of US FDA (January 9, 2015). In the US edoxaban in patients with CrCl >95 ml/min should not be used [54].

Next, Swissmedic, the regulatory authority of Switzerland, granted approval of edoxaban for stroke prevention in non-valvular AF (April 15, 2015) [55].

In the Europe EMA approved edoxaban 60 mg qd for stroke prevention in non-valvular AF in patients with CrCl >50 mL/min (June 25, 2015) [56]. Dose reduction to 30 mg qd was recommended in case of moderate or severe renal impairment (CrCL of 15 to 50 mL/min), low body weight ≤60 kg, and concomitant use of the P-gp inhibitors (ciclosporin, dronedarone, erythromycin, or ketoconazole). General warning about a trend towards decreasing efficacy of

edoxaban with increasing CrCl observed for edoxaban compared to well-managed warfarin was included with no particular CrCL cut off level mentioned [56]. Shortly after edoxaban received EMA approval the National Institute for Health and Care Excellence (NICE) in the United Kingdom issued Final Appraisal Determination on Edoxaban for preventing stroke and SE in people with non-valvular atrial fibrillation with a similar to EMA dosing approach (August 26, 2015) [57]. Importantly, several analyses confirmed the cost-effectiveness of edoxaban against warfarin for stroke prevention in AF [58, 59].

5. Laboratory monitoring

Edoxaban has a stable and predictable anticoagulant effect without the need for laboratory monitoring of coagulation. Indeed, given the results of the pivotal phase III trials with NOACs versus warfarin, i.e. non-inferiority and often superiority of the NOAC both in terms of efficacy and safety outcomes, regular laboratory control in chronic anticoagulation is not needed.

Laboratory measurement might be needed in cases of medications administered concomitantly and poor adherence to treatment or overdose. Laboratory testing may also aid decision-making on when to proceed with emergent invasive procedures or surgery, initiate thrombolytic therapy of ischaemic stroke to prevent haemorrhagic transformation, or stop haemostatic therapy to prevent prothrombotic effects [60, 61].

Despite effects of edoxaban on various coagulation parameters (e.g., PT, aPTT, INR), they are largely qualitative, and have nonlinear, exhibit wide variability and only modest correlation with edoxaban concentration [62]. For example, aPTT was elevated by average of 21% in 1.5 hour and 4% in 12 hours after edoxaban 60 mg taken orally [25] while doubling of aPTT level from baseline required drug concentration of 500 ng/ml that is more than two-fold higher compared to

maximum steady-state plasma concentration observed with edoxaban 60 mg qd regime in the phase II dose selection study [36, 63]. Better but still insufficient sensitivity was observed with PT assay [62].

Apparently, only anti-FXa activity, also used for evaluation of anticoagulation with low molecular weight heparin (LMWH), offers reliable quantification of anticoagulation with edoxaban as it exhibits linearity across a broad range of drug concentrations[60, 62]. However, there is variability with high (above therapeutic level) edoxaban concentrations. Specific calibrated plasmas are expected to further improve diagnostic accuracy of anti-FXa assay because currently available data are based on use of LMWH standards for calibration [60, 62]. Anti-FXa assays are complex, expensive and not available in most clinics routinely 24 hours a day thus far.

If anti-Xa assays are not available, a prolonged PT can be considered as evidence of circulating edoxaban. Nonetheless, PT or aPTT within normal range cannot rule out therapeutic concentration of edoxaban [62].

6. Adherence to anticoagulant therapy and real-world practice

Non-requirement for regular laboratory monitoring is also believed to affect adherence to treatment. Good adherence to treatment is essential in AF patients under oral anticoagulation irrespectively of OAC chosen. However, the short half-life of edoxaban and once daily regime pose patient even at higher risk of stroke and SE in case of one missed dose compared to NOACs with twice a day dosing regime or warfarin that is known to maintain persistent anticoagulation effect within several days after last dose has been taken [15]. Nonetheless, regular monitoring is unlikely to improve adherence significantly because even with best available assays only last

taken dose can be evaluated while INR gives estimation of warfarin activity within several days before measurement.

In the ENGAGE AF – TIMI 48 trial, there was a discontinuation rate of over 30% in both edoxaban arms and the warfarin arm, but rate of discontinuation due to non-adherence was not reported. Based on data obtained from real-world experience (that is currently lacking for edoxaban) adherence to anticoagulation seen in clinical trials does not necessarily translate to the everyday clinical practice that eventually affects treatment outcomes [40, 64]. For example in the prospective Dresden NOAC Registry primary end point of stroke or SE occurred with rate of 2.88 and 0.86 %/year in patients treated with dabigatran 110 mg bid and 150 mg bid, respectively, versus 1.54 and 1.11 % year in the RE-LY trial. The discontinuation rate was found to be higher, at 25.8% versus 21.2% and 20.7% observed in the trial with low and high dose dabigatran, respectively [65, 66]. This was consistent with the data from cohort from Veteran Affairs hospitals with 27.8% patients classified as non-adherent (proportion of days covered below 80%) and non-adherence resulted in increased risk for combined end point of all-cause mortality and stroke (HR 1.13, 95% CI 1.07-1.19 per 10% decrease in proportion of days covered) [67].

Noteworthy, real-world practice affects not only NOACs effectiveness and safety but also those of warfarin. For example, rates of stroke and major bleeding on warfarin were over three times higher among AF patients compared to those observed in the ARISTOTLE trial with apixaban: 5.29 versus 1.51 per 100 person-years for stroke and 10.78 versus 3.09 per 100 person-years for major bleeding [68]. Recent analysis of large UK cohort of anticoagulant-naïve AF patients (n=27 514) the proportion remaining on OAC at one year was significantly higher with the NOACs (79.2%) than with VKAs (63.6%). This translated to persistence rate for patients with the CHA_2DS_2-VASc score of ≥ 2 (83.0 % versus 65.3%, respectively) [69]. Also patients on

rivaroxaban from the US database had a significantly better rate of persistence compared to those on warfarin (HR 0.63, 95% CI 0.59-0.68) and lower rate of discontinuation (HR 0.54, 95% CI 0.49-0.58) [70].

Nonetheless, plenty of studies also showed consistency of real-world data with those from pivotal trials on effectiveness, safety, and adherence to anticoagulation with NOACs. FDA analysis among Medicare beneficiaries with over 134 000 patients treated with dabigatran etexilate included and followed up for 37 500 person-years showed lower risk of ischaemic stroke (HR 0.80, 95% CI 0.67-0.96); ICH (HR 0.34, 95% CI 0.26-0.46) and mortality (HR 0.86, 95%CI 0.77-0.96) when compared to AF patients taking warfarin. Higher rate of major gastrointestinal bleeding on dabigatran etexilate (HR 1.28, 95% CI 1.14-1.44), but no difference with respect to myocardial infarction (HR 0.92, 95% CI 0.78-1.08) were observed in this cohort [71]. When only anticoagulation-naïve patients were included broadly similar results were obtained. Dabigatran etexilate was associated with a lower risk of ischemic stroke or SE (HR 0.86, 95% CI 0.79-0.93), hemorrhagic stroke (HR 0.51, 95% CI 0.40-0.65), and acute myocardial infarction (HR 0.88, 95% CI 0.77-0.99), and gastrointestinal bleeding (HR 1.11, 95% CI 1.02-1.22) [72]. Also Larsen et al found similar stroke or SE and major bleeding rates as well as lower mortality, ICH, pulmonary embolism, and MI with dabigatran etexilate compared with warfarin in the large Danish nationwide cohort [73].

The prospective, observational study XANTUS (Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation) also confirmed safety and effectiveness of another NOAC, rivaroxaban, in a real-world setting. The persistence with rivaroxaban was 80% at one year in this study. The stroke and major bleeding rates were even lower (0.7% versus 1.7% and 2.1% versus 3.6% events per 100 patient-years, respectively) in this unselected patient population than in ROCKET AF trial, however patients involved in the registry had lower stroke risk than in trial ($CHADS_2$

2.0 versus 3.5, respectively) [74]. Laliberte et al did not found differences in real-world rates of composite stroke and SE and major, intracranial, or gastrointestinal bleeding with rivaroxaban and warfarin [75].

Thus, despite missing so far real-world data on edoxaban, those available for other NOACs suggest them as a safe and effective alternative to warfarin in patients with AF managed in routine practice settings. Patient education is essential for patients taking OAC to improve their compliance, efficacy and safety of therapy irrespectively of anticoagulant being used [76, 77].

7. Bleeding and antidotes

Despite lower rate of bleeding complications compared to warfarin therapy apart from gastrointestinal bleeding the risk of haemorrhage with edoxaban still exists. Both physicians and patients are concerned with the absence of specific antidote for the edoxaban and other NOACs. Thus far bleeding management includes general procedures like as local haemostasis, replacement of blood volume, discontinuation of next doses. Given relatively short half-life of edoxaban time is important curative factor with normalization of coagulation parameters achieved within one day in patients with normal renal function [78, 79].

In the case of life-threatening bleeding rapid reversal of anticoagulation effect is required. Currently only non-specific reversal agents, that were approved for warfarin-associated bleeding, e.g., prothrombin complex concentrate (PCC), activated PCC, and recombinant factor VIIa are available for urgent reversal of anticoagulant effect of edoxaban [80, 81]. The use of these agents has not been supported by clinical trials but mostly preclinical in vitro and animal models. Moreover they are associated with procoagulant and prothrombotic effects and therefore should

only be considered in patients with life-threatening bleeding, when bleeding persists despite the ongoing use of standard haemostatic measures and haemodynamic support, or when longer than usual time for drug clearance is expected. Depending on severity of bleeding four-factor or three-factor PCC in the dose of 25–50 IU/kg of body weight repeated once or twice can be chosen, while activated PCC and recombinant factor VIIa got less support [79, 81]. Local protocols addressing management of NOAC-related bleeding should be developed in hospital to facilitate patients care.

Of note, the pivotal phase III trials, including ENGAGE AF-TIMI 48, were carried out in the absence of specific antidotes, but this did not translated into worse bleeding and mortality outcomes. PCC was used, and patients on warfarin required it even more frequently.

There are two specific reversal agents for factor Xa inhibitors and one for direct thrombin inhibitor that are currently investigational [82]. Andexanet α, modified recombinant factor Xa have been developed as an antidote for factor Xa inhibitors. Andexanet α acts as a factor Xa decoy with high specificity to both oral and injectable factor Xa inhibitors in the circulation, hence, allowing intrinsic factor Xa to escape inhibition and take part in the coagulation cascade. Andexanet α is enzymatically inactive due to several modifications in comparison to normal factor Xa, for example, being unable to cause prothrombin activation and to bind to phospholipids in the prothrombinase complex. This agent works in a dose-dependent manner, and several phase III studies have been designed to study ability of andexanet α to reverse anticoagulation effect of apixaban and rivaroxaban (study with edoxaban is planning). For example, in the ANNEXA-A study with apixaban, its anticoagulant activity measured by anti-FXa activity following the administration of a bolus of andexanet α was reduced by 93.5%. The latter effect was maintained by continuous infusion of reversal agent andexanet α with anti-FXa activity reduced by 92.7% two hours post-infusion. This was accompanied with significant

reduction of apixaban plasma concentration and restoration of thrombin generation in all subjects [83]. The ANNEXA-4 trial, a single-arm confirmatory study in patients receiving apixaban, rivaroxaban, edoxaban or enoxaparin who present with an acute major bleed is now ongoing [84].

In the model of major bleeding in rivaroxaban-treated animals andexanet α was shown to reduce blood loss significantly (>80%), as well as anti-FXa activity, PT and aPTT while therapeutic dose of four-factor PCC had no impact on any of these parameters [85].

Another reversal agent ciraparantag (aripazine, PER977) is a small molecule which binds non-covalently to anticoagulants, inhibiting the anticoagulant effects of factor Xa inhibitors, direct thrombin inhibitor dabigatran, LMWH, and fondaparinux. In the phase I study in patients who were administered edoxaban a single intravenous dose of ciraparantag (100 to 300 mg) resulted in recovery of the whole-blood clotting time to within 10% above the baseline value in ten minutes, and effect persisted up to 24 hours [86]. A Phase II clinical study with ciraparantag for edoxaban reversal is currently ongoing [87].

Idarucizumab is a specific reversal agent for dabigatran etexilate [46]. It is a fully humanized mouse monoclonal antibody fragment with at least 350 times higher affinity binding specific to dabigatran than to thrombin. Interim results of an ongoing phase III RE-VERSE AD study (A Case Series Clinical Study of the Reversal of the Anticoagulant Effects of Dabigatran by Intravenous Administration of 5.0 g Idarucizumab [BI 655075] in Patients Treated With Dabigatran Etexilate Who Have Uncontrolled Bleeding or Require Emergency Surgery or Procedures) [88] showed rapid and complete reversion of the anticoagulant activity of dabigatran in 88 to 98% of patients with no safety concerns among all the study participants [89] that was consistent with a preclinical data and studies in healthy volunteers [90-92].

Thus, with availability of specific reversal agents for the NOACs anticoagulation management will become even safer and will contribute to confidence of their use. However, apparently definite protocols should be developed before reversal agents will be introduced into clinical practice, because laboratory (i.e., reversal or improvement of coagulation parameters) but not clinical (i.e., bleeding discontinuation) were used as primary study outcomes. Also due to differences in drugs pharmacology they will apparently require different regimes of reversal agents administration.

8. Warfarin, edoxaban or other NOAC?

With the idea that even one additional stroke risk factor poses patient with non-valvular AF at increased risk of stroke or SE development paradigm of stroke prevention shifted towards looking for low risk patients, i.e. those with AF and younger than 65 years. The rest simply needs effective stroke prevention with OAC [6].

In the prospective observational PREFER in AF registry (Prevention of thromboembolic events – European Registry in Atrial Fibrillation) 85.6% of patients with CHA_2DS_2-VASc score ≥2 and 70.1% of the patients with a CHA_2DS_2-VASc score of 1 received OAC reflecting implementation of the latest guidelines [93]. Notwithstanding the risk of OAC-associated bleeding patients are ready to tolerate 4.4 bleeding events to prevent one stroke [94]. However other questions arise: should we say now no to warfarin; to switch all patients to NOACs or not; and how to make an appropriate choice between range of available NOACs?

Warfarin is known to be more versatile OAC that can be used in various clinical scenarios excluded from the pivotal stroke prevention clinical trials on NOACs based on study criteria or

negative results were obtained for NOACs. Such scenarios include end-stage kidney disease (CrCl below 30 or 15 ml/min depending on NOAC), acute coronary syndromes and stenting, valvular AF including mechanical prosthetic valves [15].

For long-term OAC the major factor in favor of warfarin is a high TTR, the parameter closely associated with the quality of OAC management. The efficacy and safety of warfarin (or other VKAs) therapy are closely associated with high TTR, i.e. >70% (or >65%). Patients on warfarin in the NOACs trials had consistently good TTRs with the highest one observed in the ENGAGE AF-TIMI 48 trial but in the real-world setting TTRs tended to be lower [95]. Even patients with initially stable VKA treatment may develop extreme overanticoagulation episodically that is associated with a 2.3 times (95 % CI 2.0-2.5) higher risk for low TTR accompanied by increased risk of bleeding (HR 2.1, 95%CI 1.4-3.2), VKA-related death (HR 17.0, 95% CI 2.1-138), and thrombosis (HR 5.7, 95% CI 1.5-22.2) [96].

Pharmacogenetic studies were attempted to improve patients selection and ensure high TTR. One analysis was performed in the ENGAGE AF – TIMI 48 cohort. Based on evaluation of polymorphisms of two genes, CYP2C9 and VKORC1, involved in warfarin metabolism, patients were classified into normal responders, sensitive and highly sensitive to warfarin patients. The two latter groups had a 31% and 2.66 times higher risk of bleeding within the first 90 days of treatment when compared with normal responders, respectively [97]. However genotyping showed only marginal improvement compared to standard of care. In a recent meta-analysis evaluated two approaches genotype-guided OAC improved TTR in comparison to fixed VKA dosing algorithms, but not with clinical algorithms, and it did not result in decreased composite of death, thromboembolism and major bleeding [98].

The SAMe-TT_2R_2 score was developed and validated in several cohorts to aid identifying patients with non-valvular AF who were expected to stay within therapeutic window and maintain a high average TTR with VKA (Table 5) [8, 99]. While the score was increasing from 0 to ≥4 progressive decline of TTR from 67.5±24.6% to 52.7±28.7% was observed [100]. Despite moderate discrimination ability (c-statistic of 0.57) it allows in simple and practical way to distinguish the best candidates for OAC with warfarin, vs a NOAC. A SAMe-TT_2R_2 score of ≥2 was associated with 1.64 (95 % CI 1.33–1.95) probability of low TTR. The ability of the stratification scheme to predict low TTR translated to its prognostic value for both stroke/SE and severe bleeding events [101]. The SAMe-TT_2R_2 score also allows avoiding of practice of 'trial period with VKAs' or 'VKA stress test', which often place patients at unnecessarily high risk of thromboembolic or bleeding complications [102].

One more important issue is a patient's warfarin status. In the prespecified analysis of the ENGAGE AF – TIMI 48 trial high dose edoxaban appeared to be superior to warfarin for stroke and SE prevention in VKA-naïve patients (HR 0.71, 95% CI 0.56-0.90) but only non-inferior in VKA-experienced patients. Low dose edoxaban was similar to warfarin for stroke or SE prevention in patients who were VKA-naïve, but inferior VKA-experienced patients (HR 1.31, 95% CI 1.08-1.60) [103]. Also, patients with history of stroke are prone to have lower TTR and higher bleeding risk, and thus, NOACs are likely to be beneficial in these patients [104].

The data from the NOACs trials were pooled in several systematic reviews and meta-analyses of which two included also data on edoxaban [105, 106]. NOACs were found to be superior to warfarin with respect to prevention of stroke and SE, haemorrhagic stroke, ICH, and all-cause mortality; non-inferior with respect to rate of ischaemic stroke and myocardial infarction. There was a trend towards reduced risk of major bleeding but more episodes of gastrointestinal bleeding were observed.

Thus, NOACs gained priority over VKAs in the European guidelines, but no preference was given to either of them in the American guidelines. European guidelines allow dual antiplatelet therapy of aspirin and clopidogrel for patients who deny OAC. Obviously such a therapy is inferior to OAC, including edoxaban, that was confirmed in indirect comparison analysis by Blann et al [77]. In the latter analysis, edoxaban 60 mg qd was associated with lower risk of stroke (relative risk [RR] 0.62, 95% CI 0.46-0.82), ischaemic stroke (RR 0.53, 95% CI 0.38-0.73), and SE (RR 0.21, 95% CI 0.08-0.54) while trend in favor of edoxaban was observed for death (RR 0.88, 95% CI 0.74-1.05) and ICH (RR 0.64, 95% CI 0.35-1.2) [107].

There were also several indirect comparison analyses performed evaluated NOACs, two of which included edoxaban [108, 109]. Despite all phase III trials used warfarin as an active comparator and all were performed in patients with non-valvular AF, the still had dissimilarities in methodology and patients characteristics that eventually might affect results of such an indirect comparison [40].

Dabigatran 150 mg bid was found to be superior to high dose edoxaban for prevention of such end points as stroke and SE (HR 0.75, 95% CI 0.56–0.99), stroke (HR 0.73, 95% CI 0.55–0.96), and haemorrhagic stroke (HR 0.48, 95% CI 0.23–0.99). There were more major bleedings with rivaroxaban (HR 1.30, 95% CI 1.08–1.57) but less major or clinically relevant non-major bleedings and gastrointestinal bleedings with apixaban (HR 0.79, 95% CI 0.70–0.90) compared to high dose edoxaban [109]. Low dose edoxaban appeared to be less effective for stroke and SE, any stroke and ischaemic stroke than all NOACs apart from dabigatran 110 mg bid. However low dose edoxaban was associated with significantly reduced rate of major bleeding (compared to all NOACs) and gastrointestinal bleeding (compared to all NOACs with exception

of apixaban) [109]. All the NOACs showed equal efficacy for reduction of cardiovascular and all-course mortality and safety with respect to ICH risk [109].

Taking into account extensive discussion of anticoagulant effect of the NOACs in patients with kidney impairment, all of them had similar efficacy and safety compared to warfarin across different levels of kidney function, but edoxaban and apixaban were associated with better safety profile. However, these results were also derived from indirect comparison analyses [110].

Have clinicians got the chance to tailor anticoagulation regimen to each individual patient? Apparently, such a selection based on indirect comparison analyses is largely speculative because of different trial cohorts. Indirect comparisons were performed to generate hypothesis which are unlikely to be tested in randomized clinical trials in near future. Huge data are necessary to collect to power the study with NOACs against each other, given their safety and efficacy obtained in the pivotal phase III trials.

Thus far, high dose dabigatran, given its superiority over warfarin for ischaemic stroke and SE prevention (HR 0.65, 95% CI 0.52-0.81) and ischaemic (or uncertain) stroke prevention (HR 0.76, 95% CI 0.60-0.98) might be considered in patients with the high CHA_2DS_2-VASc score, but in patients without dyspepsia since the latter is known to be the most common side effect and reason for non-adherence and discontinuation [46].

In patients with a high bleeding risk (HAS-BLED score of ≥3) the NOACs associated with lower risk of major bleeding, i.e. low dose dabigatran (HR 0.80, 95% CI 0.70-0.93), apixaban (HR 0.69, 95% CI 0.60-0.80), edoxaban (HR 0.80, 95% CI 0.71-0.91), are preferred [6, 15]. In patients with a history or risk of gastrointestinal bleeding apixaban might be recommended, since it did not result in increased gastrointestinal bleeding risk in the phase III trial. Patient's

preferences to once daily dosing should be considered, and either rivaroxaban or edoxaban can be administered.

9. Uncovered areas

There are common clinical settings which may occur in patients with AF, but they were excluded from the ENGAGE AF – TIMI 48 trial because of study criteria, real-world experience because of recent approval is also lacking. This at least includes anticoagulation in patients with concomitant coronary heart disease and undergoing stenting, pericardioversion and periablation anticoagulation.

Minimal duration of 3 weeks prior (unless absence of left atrial appendage thrombus is confirmed by transoesophageal echocardiography) and 4 weeks after cardioversion to prevent thromboembolic complications. In the X-VeRT trial (Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation) rivaroxaban showed the similar to warfarin rate of combination of stroke, TIA, SE, myocardial infarction and cardiovascular death. The rate of major bleeding was comparable too. The major advantage was significantly shorter time to cardioversion driven by long time spent for achievement of stable INRs in the warfarin arm [111]. Consistent results were obtained in the post-hoc analyses of phase III trials with rivaroxaban, apixaban, and dabigatran [15]. The largest cardioversion trial is ENSURE-AF (Edoxaban vs. warfarin in subjects undergoing cardioversion of atrial fibrillation), with 2200 patients planned to be randomized edoxaban or warfarin and 2000 cardioversions performed [112]. This trial is ongoing now with results expected in 2016.

Catheter ablation of AF is also known to require OAC prior and after procedure. In the VENTURE-AF trial randomized patients undergoing catheter ablation of AF to uninterrupted consistently low rate of thromboembolic and bleeding events was observed [113]. Safety and efficacy profile was observed to be broadly similar for dabigatran versus warfarin [46], and also were addressed in the RE-CIRCUIT trial (Randomized evaluation of dabigatran etexilate compared to warfarin in pulmonary vein ablation: assessment of different peri-procedural anticoagulation strategies) [114].

Finally, approximately 20% to 35% of AF patients also have coronary artery disease irrespectively of AF type, e.g., new onset, paroxysmal, persistent, and permanent. Up to half of these patients also develop myocardial infarction and/or undergo coronary stenting [115]. There was no increased risk of myocardial infarction in edoxaban arms of the ENGAGE AF – TIMI 48 trial [39] as it was with dabigatran in the RE-LY trial [46], hence, edoxaban provides sufficient prevention of coronary events in stable patients. In patients with acute coronary syndrome and after stent implantation dual antiplatelet therapy (i.e. aspirin and clopidogrel) is needed to complement OAC (triple antithrombotic therapy), since either of them is not sufficient alone to prevent stroke and SE on the one hand, and stent thrombosis on the other.

Current recommendations are based on experts consensus and do not advise to change NOAC to warfarin if this regime of OAC has been already well established. There is also no guidance for OAC selection in patients with new onset AF. Given that triple antithrombotic therapy is associated with significantly increased bleeding risk, lower available dose of NOAC should be used [116, 117].

In the small exploratory trial X-PLORER rivaroxaban caused suppression of coagulation activation as assessed with the levels of prothrombin fragments 1+2 and thrombin–antithrombin

complex in AF patients with CAD requiring elective percutaneous coronary intervention [118]. Two trials involving NOACs in AF patients treated with percutaneous coronary intervention are currently recruiting participants: the REDUAL-PCI trial comparing dual antithrombotic therapy regimen of dabigatran 110 mg bid or 150 mg bid plus clopidogrel or ticagrelor with a triple antithrombotic therapy of warfarin plus clopidogrel or ticagrelor plus low dose aspirin, and the PIONEER AF – PCI trial evaluating rivaroxaban 2.5 mg bid plus low-dose aspirin 75-100 mg qd and clopidogrel 75 mg qd (or prasugrel 10 mg qd, or ticagrelor 90 mg bid) followed by rivaroxaban 15 mg (or 10 mg for individuals with moderate renal impairment) qd plus low-dose aspirin for 12 months compared to the same regime but with dose-adjusted VKA instead of rivaroxaban [119, 120]. Other similar trials with apixaban and edoxaban have been announced.

10. Conclusion

In terms of efficacy and safety edoxaban is at least non-inferior to warfarin but also has important advantages which make edoxaban a favourable and convenient option for long-term anticoagulant treatment in non-valvular AF instead of less convenient warfarin. While currently available evidence is represented by the large phase III ENGAGE AF – TIMI 48 trial mostly, many clinical scenarios that may occur in patients with AF requiring anticoagulation were omitted due to exclusion criteria.

Following the approval of edoxaban data from ongoing and future trials as well as real-world registries will improve the knowledge on how to manage oral anticoagulation with edoxaban in routine clinical practice.

11. Expert opinion

AF only rarely presents without other comorbidities or risk factors of thrombosis that essentially elevates risk of stroke and/or SE in this group of patients. Moreover strokes developing at a background of AF are known to be more severe and to have worse outcomes (e.g., higher probability of lethal outcome, more likely to develop recurrent stroke, more disabling, greater cognitive loss). Effective stroke prevention in AF means OAC, with benefit significantly exceeded risk of bleeding in patients with ≥1 stroke risk factors.

Edoxaban is one of the non-vitamin K antagonist oral anticoagulants (NOACs), which were developed and introduced into clinical practice to improve management of AF patients by omitting major drawbacks of vitamin K antagonists, e.g. warfarin. Edoxaban as other NOACs has predictable anticoagulation effect with fixed dosing regime, fast onset and offset of action, non-requirement for laboratory monitoring, minor drug and food interactions.

Low dose regime (30 mg qd) and high dose regime (60 mg qd) of edoxaban both appeared to be non-inferior to well-adjusted warfarin therapy in terms of stroke and SE prevention as assessed in the intention-to-treat analysis of the ENGAGE AF – TIMI 48 trial, but trend toward superiority was found for high dose edoxaban. Edoxaban also was found to be a safe drug with consistently lower rate of major bleeding, major and clinically relevant non-major bleeding and any bleeding. Only the risk of gastrointestinal bleeding was increased with high dose edoxaban that was obviously related to its pharmacokinetics. Both edoxaban dosages were associated with reduced risk cardiovascular mortality and intracranial haemorrhage.

Nonetheless, the introduction of a new OAC drug in such a challenging area as oral anticoagulation raises new questions and not all of them have been answered thus far. There are common for all the NOACs issues of their use. Non-requirement of regular laboratory control is considered widely as one of factors amenable for lower adherence to treatment that given the

quick drug clearance may eventually lead to increased risk of stroke and SE. In the situation when degree of hypocoagulation can be measured reliably only with anti-factor Xa assay that is complex, expensive and not available in most institutions 24 hours a day, adherence is the key link between medical practice and patient outcome. Patients' education therefore is of paramount importance to obtain as effective and safe anticoagulation as it was in the landmark trial. This might make anticoagulation with edoxaban even more beneficial since in patients who remained on treatment in the ENGAGE AF – TIMI 48 superiority over warfarin was observed. However real-world data do not always reflect precisely effects achieved in the highly selected cohort of clinical trial, and no results from everyday routine clinical practice are available thus far.

One more issue shared with drugs in class is absence of clinically approved specific reversal agent that is may be necessary in case of life-threatening situations, e.g. haemorrhagic shock or when surgical intervention cannot be postponed. In less severe cases, time because of short half-life time of edoxaban (and other NOACs) can be the major curative 'agent'. Despite specific antidotes to edoxaban being desirable it is necessary to underline the fact that they were not available during testing in clinical trials but edoxaban was safer then well-managed warfarin. Knowledge of availability of specific antidote may improve the perception of edoxaban, both by patients and physicians and further improve adherence and outcomes.

Kidney function is the important factor determining edoxaban exposure. Both moderate to severe reduction of eGFR (<50 ml/min), resulting in higher drug exposure and normal to mildly reduced eGFR (>80 ml/min), resulting in lower drug exposure, eventually affect effectiveness and safety of anticoagulation with edoxaban. Hence careful initial evaluation of kidney function and repetitive measurement during follow-up are essential to guide patient management. Appropriately adjusted doses were effective and safe in patients with suboptimal kidney function as confirmed in the ENGAGE AF-TIMI 48 trial.

Anticoagulation effect is also determined by such a pharmacokinetic characteristics that depends on frequency of drug intake, i.e. once or twice a day. Edoxaban showed even better safety and effectiveness with once a day dosing regime than the same daily dose divided into twice a day intake. Once a day dosing without tradeoff between safety and effectiveness may be additional favorable factor influencing on choice of edoxaban.

The abovementioned limitations did not translate into worse clinical outcomes compared to warfarin. With the approval of edoxaban a new alternative both to vitamin K antagonists and other NOACs for stroke prevention in non-valvular AF has become available. Notwithstanding large experience obtained from phase 3 clinical trial with edoxaban versus warfarin for oral anticoagulation, some narrower areas are lacking firm evidence to date, e.g., pericardioversion and periablation use of edoxaban in patients with AF or in those with coronary heart disease undergoing stenting in either primary or elective setting. Ongoing and future trials and registries will resolve these current controversies in clinical practice.

12. Declaration of interest

GYH Lip has been a consultant for Bayer, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo and has been on the speakers bureau for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. MS Dzeshka has no conflicts of interest to declare. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents, received or pending, or royalties.

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Table 1. Stroke and bleeding risk stratification with the CHA_2DS_2-VASc [9] and HAS-BLED [12] scores

CHA_2DS_2-VASc	Score	HAS-BLED	Score
Congestive heart failure/LV dysfunction	1	Hypertension (systolic blood pressure >160 mmHg)	1
Hypertension	1	Abnormal renal or liver function	1 or 2
Age ≥75 years	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency or predisposition	1
Stroke/TIA/TE	2	Labile INRs (if on warfarin)	1
Vascular disease (prior MI, PAD, or aortic plaque)	1	Age (e.g., >65, frail condition)	1
Aged 65–74 years	1	Drugs (e.g., concomitant antiplatelet or NSAIDs) or alcohol excess/abuse	1 or 2
Sex category (i.e. female gender)	1		
Maximum score	9		9

CHA_2DS_2-VASc: heart failure [moderate-to-severe left ventricular systolic dysfunction refer to left ventricular ejection fraction ≤40% or recent decompensated heart failure requiring hospitalization], hypertension, age ≥75, diabetes, stroke/transient ischaemic attack [TIA], vascular disease [specifically, MI, complex aortic plaque and peripheral artery disease], age 65–74 years, female sex.

HAS-BLED: uncontrolled hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly [e.g. age >65, frail condition], drugs [e.g., antiplatelet, non-steroidal anti-inflammatory drugs]/excessive alcohol.

INR, international normalized ratio; LV, left ventricular; MI, myocardial infarction; NSAIDs, non-steroidal anti-inflammatory drugs; TIA/TE, transient ischemic attack/thromboembolism; PAD, peripheral artery disease.

Table 2. Pharmacological characteristics of edoxaban versus warfarin [54, 56, 121]

Parameter	Warfarin	Edoxaban
Mechanism of action	Inhibition of VKORC1	Factor Xa inhibitor (free or bound), reversible
Onset of action	Slow, indirect inhibition of clotting factor synthesis	Fast
Offset of action	Long	Short
Absorption	Rapid	Rapid
Bioavailability, %	>95	62
T_{max}, hour	2-4	1-2
V_d, L	10	107
Protein binding, %	99	55
$T_{1/2\beta}$, hour	40	10-14
Renal clearance	None	50
Non-renal clearance	None	50
CL/F, L/hour	0.35	22
Accumulation in plasma	Dependent on CYP2C9 metabolic efficiency	None (accumulation ratio 1.14)
Food effect	No effect on absorption; dietary vitamin K influence on pharmacodynamics	None
Age	Yes, lower CL/F as age increases	None (adjusted for body weight and kidney function)
Body weight	Yes, higher dose for increased weight	Yes, increased total exposure in patients with low body weight (median 55 kg) vs. high body weight (median 84 kg)
Sex	Yes, lower CL/F in women	None (adjusted for body weight)
Ethnicity	Lower dose in Asian patients; higher dose in African-American patients	Similar exposure in Asian and non-Asian patients
Drug transporter	None	P-gp

CYP-mediated metabolism	CYP2C9, CYP3A4, CYP2C19, CYP1A2	Minimal (CYP3A4)
Drug-drug interactions*	Numerous	Potent P-gp inhibitors (no dose reduction†) and inducers (avoid)
Coagulation measurement	INR	Anti-FXa is preferred method Changes in PT, aPTT, INR are highly variable
Reversal agents	Vitamin K (slow reversal, prolonged inhibition), FFP or PCCs (rapid reversal)	Andexanet, aripazine (investigational) PCCs, recombinant FVIIa
Dosing for AF	Individualised for each patient according to INR response (0.5-16 mg qd)	60 mg qd in patients with CrCl of >50 to ≤ 95 mL/min. 30 mg qd in patients with CrCl of 15 to 50 mL/min‡

AF, atrial fibrillation; aPTT, activated partial thromboplastin test; CL/F, apparent clearance; CrCl, creatinine clearance; CYP, cytochrom P450 isozymes; F, factor; FFP, fresh frozen plasma; INR, international normalized ratio; qd, once daily; PCC, prothrombin complex concentrate; P-gp, Permeability glycoprotein; PT, prothrombin time; T_{max}, time to maximum plasma concentration; $T_{1/2\beta}$, terminal half-life, V_d, volume of distribution; VKORC1, vitamin K epoxide reductase enzyme subunit 1.

* P-gp inhibitors include verapamil, amiodarone, quinidine, and certain macrolide antibiotics (e.g., erythromycin, azithromycin, and clarithromycin). P-gp inducers include rifampicin, St. John's wort (Hypericum perforatum), carbamazepine, and phenytoin. Potent inhibitors of CYP3A4 include azole antifungals (e.g., ketoconazole, intraconazole, voriconazole, posaconazole), chloramphenicol, clarithromycin, and protease inhibitors (e.g., ritonavir,

atanazavir). Potent CYP3A4 inducers include phenytoin, carbamazepine, phenobarbital, and St. John's wort.

† US edoxaban labelling; reduced dose of 30 mg qd is recommended according to European edoxaban labelling

‡ US edoxaban labelling; edoxaban 30 mg qd is recommended for patients with one or more of the following clinical factors: moderate or severe renal impairment (CrCL 15–50 mL/min), low body weight (≤ 60 kg), P-gp inhibitors (ciclosporin, dronedarone, erythromycin, ketoconazole) concomitantly according to European edoxaban labelling

Table 3. Summary of efficacy and safety of edoxaban in pivotal ENGAGE AF – TIMI 48 trial in patients with non-valvular AF [39]

Characteristics	Warfarin	Low dose edoxaban 30 (15) mg qd	High dose edoxaban 60 (30) mg qd
Patients	7036	7034	7035
Age, years	72	72	72
Mean $CHADS_2$ score	2.8	2.8	2.8
Prior vitamin K antagonist treatment, %	58.8	59.2	58.8
Prior stroke or transient ischemic attack, %	28.3	28.5	28.1
Mean TTR, warfarin arm; %	68.4	NA	NA
Discontinuation rate, %	34.5	33.0	34.4
End points, % of patients/year, HR (95% CI)			
Stroke or systemic embolism	1.69	1.91 1.13 (0.96-1.34)	1.49 0.87 (0.73-1.04)*
Ischaemic stroke	1.25	1.77 1.41 (1.19-1.67)	1.25 1.00 (0.83-1.19)
Haemorrhagic stroke	0.47	0.16 0.33 (0.22-0.50)	0.26 0.54 (0.38-0.77)
Systemic embolism	0.12	0.15 1.24 (0.72-2.15)	0.08 0.65 (0.34-1.24)
All-cause mortality	4.35	3.80 0.87 (0.79-0.96)	3.99 0.92 (0.83-1.01)
Cardiovascular mortality	3.17	2.71 0.85 (0.76-0.96)	2.74 0.86 (0.77-0.97)
Myocardial infarction	0.75	0.89 1.19 (0.95-1.49)	0.70 0.94 (0.74-1.19)
Major bleeding	3.43	1.61 0.47 (0.41-0.55)	2.75 0.80 (0.71-0.91)
Major or clinically relevant nonmajor bleeding	13.02	7.97 0.62 (0.57-0.67)	11.10 0.86 (0.80-0.92)

Intracranial hemorrhage	0.85	0.26 0.30 (0.21-0.43)	0.39 0.47 (0.34-0.63)
Gastrointestinal bleeding	1.23	0.82 0.67 (0.53-0.83)	1.51 1.23 (1.02-1.50)
Any bleeding	16.4	10.68 0.66 (0.62-0.71)	14.15 0.87 (0.82-0.92)

* 97.5% confidence interval was used

CI, confidence interval; HR, hazard ratio

Table 4. Consistency of results on the efficacy and safety of edoxaban across patient subgroups [54]

Subgroups	Outcomes	Stroke and systemic embolism			Major bleeding		
		Warfarin %/year	Edoxaban %/year	HR (95% CI)*	Warfarin %/year	Edoxaban %/year	HR (95% CI)*
Age	<65	1.11	1.05	0.94 (0.65-1.36)	1.81	1.45	0.80 (0.58-1.11)
	≥65 to <75	1.78	1.58	0.89 (0.68-1.16)	3.28	2.40	0.74 (0.58-0.93)
	≥75	2.31	1.91	0.83 (0.66-1.04)	4.67	3.90	0.84 (0.70-1.00)
Gender	Male	1.68	1.45	0.87 (0.71-1.07)	3.4	2.84	0.84 (0.72-0.99)
	Female	2.00	1.76	0.87 (0.69-1.11)	3.29	2.39	0.73 (0.58-0.91)
Weight	≤60	2.91	2.53	0.88 (0.58-1.31)	4.44	2.95	0.67 (0.45-1.01)
	>60	1.69	1.47	0.87 (0.73-1.03)	3.26	2.65	0.82 (0.71-0.94)
Stroke risk ($CHADS_2$ score)	2	1.20	1.19	0.99 (0.76-1.29)	2.78	2.05	0.74 (0.60-0.91)
	≥3	2.39	1.91	0.80 (0.66-0.97)	3.94	3.28	0.84 (0.71-0.99)
Kidney function (CrCl, mL/min)	<30	2.61	2.41	-	5.07	3.83	0.76 (0.58-0.99)
	30-50	2.70	2.34	0.87 (0.64-1.19)	3.49	3.08	0.88 (0.73-1.07)
	>50-80	2.17	1.49	0.68 (0.54-0.86)	2.85	2.44	0.86 (0.60-1.22)
	>80	0.97	1.28	1.33 (0.97-1.81)	2.26	1.32	0.59 (0.41-0.84)
Prior history of stroke/TIA	Yes	2.85	2.44	0.86 (0.67-1.09)	3.56	3.06	0.87 (0.68-1.10)
	No	1.41	1.24	0.88 (0.72-1.08)	3.29	2.53	0.77 (0.66-0.90)
Prior diabetes	Yes	1.52	1.42	0.94 (0.71-1.25)	3.83	2.97	0.78 (0.63-0.96)
	No	1.96	1.65	0.84 (0.70-1.02)	3.10	2.52	0.81 (0.69-0.96)
Warfarin at randomisation	VKA-experienced	1.60	1.62	1.01 (0.82-1.24)	3.28	2.58	0.79 (0.67-0.93)
	VKA-naïve	2.12	1.49	0.71 (0.56-0.90)	3.49	2.83	0.82 (0.67-1.00)
Aspirin at randomisation	Yes	2.23	1.54	0.70 (0.53-0.92)	4.62	3.50	0.76 (0.62-0.94)
	No	1.63	1.58	0.97 (0.80-1.17)	2.86	2.35	0.82 (0.70-0.97)

* HR <1.0 in favor of edoxaban, >1.0 in favor of warfarin

Table 5. Quality of anticoagulation control assessment with the SAMe-TT_2R_2 score [99]

Sex category (i.e. female gender)	1
Age <60 years	1
Medical history (≥2 of the following: hypertension, DM, CAD/MI, PAD, CHF, previous stroke, pulmonary, hepatic or renal disease)	1
Treatment with interacting drugs(e.g., amiodarone)	1
Tobacco use (within 2 years)	2
Race (i.e. non-caucasian)	2

CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; MI, myocardial infarction; PAD, peripheral artery disease